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Unusual presentation of more common disease/injury

Antiphospholipid syndrome and recurrent thrombosis – limitations of current treatment strategies

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Summary

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder that is characterised by the presence of antiphospholipid antibodies and a common cause of vascular thromboembolic phenomena. The management of patients with APS is currently directed to antithrombotic medications. The international therapeutic guidelines recommend oral anticoagulation with warfarin indefinitely after the first thrombotic episode. However, therapeutic guidelines lack for a minority group of patients – the patients appropriately anticoagulated with recurrent thromboembolic phenomena. The authors present a clinical report that reveals the therapeutic and diagnostic complexity of this specific group of patients. Regarding recent studies, APS has been revealed as a complex syndrome with multiple pathophysiological mechanisms previously unknown. In this context, new therapeutic approaches have been defended and empirically experienced, with potentially promising results.

BACKGROUND

Antiphospholipid syndrome (APS) or Hughes syndrome was first described in 1983 by Hughes.[1]

Although only thrombotic phenomena and recurrent spontaneous abortion are included in the classification reviewed in 2006,[2] many other clinical features are known to be associated with APS. These include valvular heart disease, livedo reticularis, thrombocytopenia, nephropathy and specific neurological manifestations.[3] The spectrum of clinical manifestations associated with APS, revealing itself as a complex entity, has contributed to the development of multiple clinical studies. The scientific progress in the understanding APS's pathophysiological mechanisms has provided new perspectives for a more effective therapeutic approach in these patients.

The current therapeutic guidelines are based on long time anticoagulation for secondary prevention after a first thrombotic episode. There is consensus in oral anticoagulation with warfarin, in order to achieve an international normalised ratio (INR) target of between 2.0 and 3.0.[4]

In patients with APS anticoagulated with warfarin and with thrombosis recurrence, the therapeutic approach currently advocated clearly shows that we are in need for new, safer and more efficacious treatment modalities. The authors describe a clinical report that reveals the diagnostic and therapeutic difficulties related to this specific group of patients.

CASE PRESENTATION

We describe a 60-year-old caucasian male patient with a known history of APS. The diagnosis was made 6 years earlier, after massive bilateral pulmonary thromboembolism. Blood tests revealed elevated levels of antiphospholipid autoantibodies in two determinations with 3-month intervals (positive lupus anticoagulant, anticardiolipin antibodies and β2 glycoprotein 1 (GPI)) and elevated inflammatory parameters (erythrocyte sedimentation rate (ESR) 35 mm/h and C reactive protein of 3.6 mg/dl).

An additional screening for thrombophilia was carried out, which was negative (Factor V Leiden variant, prothrombin mutation, Factor VIII levels, methylenetetrahydrofolate reductase mutation, protein C, free and total protein S, factor VIII, antithrombin, plasminogen, tissue plasminogen activator plasminogen activator inhibitor and-1.

Since then, after resolution of the initial thrombotic event, he remained asymptomatic on warfarin anticoagulation with a target INR between 2 and 3.

His personal history included Parkinson's disease and benign prostatic hyperplasia, medicated.

The patient was seen in our department and subsequently hospitalised with pleuritic, left anterior chest pain, dyspnoea on moderate exertion and haemoptoic productive cough. He had these symptoms for about 1 week. No fever or constitutional symptoms were present.

On examination, the patient was afebrile and eupneic at rest. Cardiac and pulmonary auscultation revealed no abnormalities. Clinical examination was unremarkable.

INVESTIGATIONS

Blood tests showed an ESR of 55 mm/h and INR of 4.4, no anaemia or leukocytosis; Prostate-specific antigen was in the normal range – 1.2 ng/ml.

A chest radiograph revealed a nodular lesion with 3 cm in diameter, located in the middle lobe of left lung (figure 1).

For clarification of the radiological abnormalities, a lung CT scan was performed which showed a mass lesion with irregular contours, with extensive pleural deployment and bronchial involvement. CT scan images had changes imposing differential diagnosis with cancer, not excluding pulmonary infarction (figure 2).

Figure 1 Chest radiograph revealing a nodular lesion located in the middle lobe of left lung.

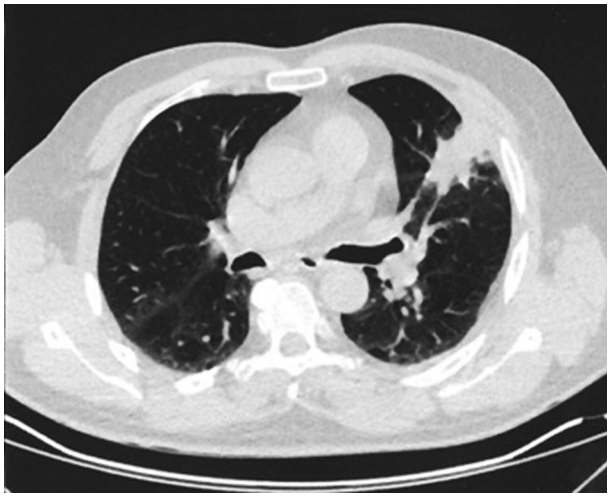

Figure 2 Lung CT scan images showing a mass lesion with irregular contours with extensive pleural deployment and bronchial involvement.

DIFFERENTIAL DIAGNOSIS

Considering the differential diagnosis of lung cancer and pulmonary infarction, a ventilation/perfusion scanning was performed and showed a high probability of pulmonary embolism.

The patient also performed an echocardiogram that excluded right ventricular dysfunction.

Bronchoscopy showed no evidence of direct signs of malignancy. Histological examination was negative for neoplastic cells.

TREATMENT

Following the results obtained, the patient was treated with low-molecular-weiht-heparin in therapeutic dose despite having an INR value of 4.4, with progressive disappearance of the initially abnormalities found on CT (figure 3A,B).

After resolution of acute episode, the patient was treated with high intensity warfarin medication, with an INR between 3 and 4. Treatment with statin was associated.

Some additional thrombotic risk factors were controlled, namely, a sedentary lifestyle, overweight and hyperlipidaemia.

OUTCOME AND FOLLOW-UP

After 2 years of follow-up, the patient was diagnosed with prostate cancer, having undergone total prostatectomy.

Currently, he presents no symptoms and no recurrence of thrombosis.

DISCUSSION

The diagnosis of APS is considered when a clinical criterion – vascular thrombotic events or pregnancy morbidity – is associated with some specific abnormal laboratory tests – analytical positivity for antiphospholipid antibodies.[5] In these patients the risk of arterial or venous thrombosis is increased, as well as its recurrence.[6]

Several studies have shown that additional prothrombotic risk factors may be associated with an increased risk for thrombosis in patients with antiphospholipid antibodies.[7] A recent prospective study found that 50% of patients with APS had coincident risk factors for thrombosis at the time of a first thrombotic event.[8] Appropriate treatment of additional prothrombotic risk factors that can be modified in patients with antiphospholipid antibodies is essential to minimise the associated thrombotic risk.

A variety of risk factors have been identified to be linked to thrombotic events, including immobilisation during prolonged travel, obesity, smoking, surgery, trauma, oral contraceptives and postmenopausal hormone replacement. Medical conditions that increase the risk of thromboembolism include cancer and APS. Some genetic risk factors, including factor V Leiden and the prothrombin G20210A mutation, have been identified, but they account for only a minority of thromboembolic disease.[9]

As a result of the prothrombotic state in APS, anticoagulation medication has been logically the mainstay of the treatment of this disease. However, some dilemmas exist regarding the optimal management of the different categories of APS patients.

The therapeutic approach after a first thrombotic episode is based on long-term anticoagulation, including oral anticoagulation with moderate-intensity warfarin to achieve target INR of 2.5. The duration of anticoagulant therapy should be decided on an individual basis, according to a multi-factorial risk assessment.[10] Current recommendations from the American College of Chest Physicians (ACCP) for treatment of patients with APS after an episode of venous thrombosis is anticoagulation with warfarin with target INR value of 2.5 (level 1A) for 12 months (level 1C +). It should also be considered for indefinite anticoagulation (level 2C).[4]

The authors present a clinical report where, despite the long-term anticoagulant therapy, with values above recommendations, new thrombosis occurred 6 years after beginning treatment with warfarin. They reported that the patient was diagnosed with pulmonary infarction, had an INR of 4.4, and thus is included in the minority of patients in whom thrombotic events recur despite adequate anticoagulation.

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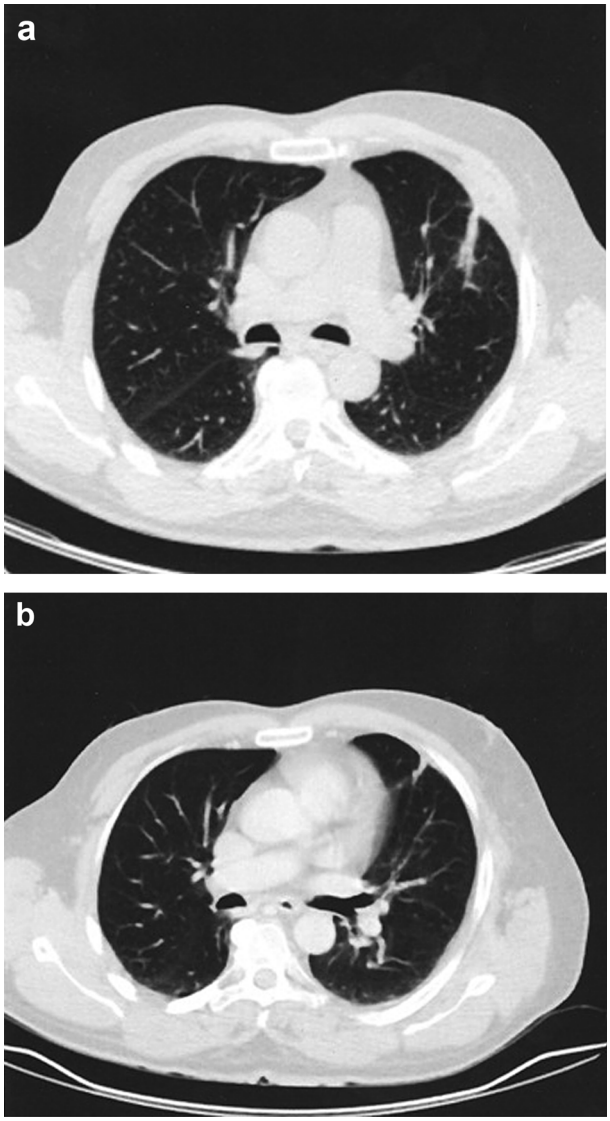

Figure 3 (A, B) Lung CT scan images showing disappearance of the inicial lesion, after treatment with heparin in therapeutic dose.

The acute thrombotic episode was resolved with low-molecular-weight-heparin in accordance with ACCP recommendations for the initial treatment of pulmonary embolism (level 1A).[4] In addition to the therapeutic recommendations, the use of heparin can avoid the inherent variations of INR associated to warfarin, ensuring adequate anticoagulation since the beginning of treatment.

The optimal treatment of thrombosis in patients with APS requires assessment of thrombosis risk associated with antiphospholipid antibodies so that the potential benefits of antithrombotic therapies for preventing thrombosis can be balanced against the risk of bleeding.[6]

With respect to the intensity of anticoagulation, several retrospective studies find few or no recurrences when INR is over 3. Anticoagulation with an INR over 3 should be reserved for those cases in which venous thrombosis recurrence has occurred while under an INR between 2 and 3.[11]

British society of Haematology recommends an INR target of 2.5 for patients with venous thrombosis associated to APS. A higher target of 3.5 is often used and is considered reasonable as long as the bleeding risk at the higher intensity of anticoagulation is taken into consideration. A target of 3.5 is also recommended for patients who suffer recurrence of VTE while on warfarin with an INR between 2.0 and 3.0.[12]

The fact that the patient experiences at thrombotic diagnosis an INR of 4.4 does not necessarily mean that pulmonary infarction occurred at this INR value, given that the onset of symptoms was 1 week before. So, our option was to maintain this patient on warfarin, but with higher target INR, controlling the bleeding risk. Additional thrombotic risk factors were also eliminated.

Factors that may increase the risk of haemorrhage during oral anticoagulant therapy include age greater than 65 to 75 years, receiving multiple medications, history of gastrointestinal tract bleeding, arterial thrombosis or stroke and INRs higher than 4.5 to 5.0.[13] The described patient did not have any of these bleeding risk factors.

The prostate cancer only diagnosed 2 years later could be another thrombosis risk factor in this patient.

Some studies have shown a minimal likelihood of recurrence of thrombotic events in patients with APS, under moderate intensity treatment with warfarin (with an INR between 2 and 3). Derksen *et al* reported a zero probability of thrombotic recurrence after 8 years of oral anticoagulation maintained.[14] In the study published by Khamashta *et al*, only 10% of patients with APS anticoagulant therapy with warfarin in therapeutic INR values of 3, had recurrent arterial or venous thrombotic events over 5 years.[15]

The lack of precise guidelines hampers treatment of these patients uncertain and challenging.

Two recent randomised studies (Crowther *et al* and Finazzi *et al*) comparing different intensities of anticoagulation (a target INR of 2.5 comparing to a target higher than 3.0) concluded that a target INR of 2.5 was sufficient for treatment of patients with thrombosis in association with APS.[16 17]

Besides lack of evidence-based data, some international guidelines accept that the therapeutic strategy in patients with recurrent thrombosis while on warfarin, could be based on a higher target INR (between 2.5–3.5 or 3.0–4.0).[12]

Other possible treatment options for recurrent thrombosis despite warfarin are switching from warfarin to therapeutic doses of unfractionated heparin or low-molecular-weight heparin, or adding an antiplatelet agent to warfarin.[6] Dabigatran etexilate, a direct thrombin inhibitor, and rivaroxaban, the first in a new class of drugs, the oral direct factor Xa (FXa) inhibitors, are both fixed-dose orally administered agents and may be potential drugs in APS thrombosis treatment.[18] Plasma exchange or intravenous immune globulin, particularly in patients with catastrophic APS, has also been suggested.[6]

Especially in secondary APS cases, associated with another autoimmune disease, an immunomodulatory strategy could be considered. Immunomodulatory therapies that have been anecdotally used in patients with APS include steroids, cyclophosphamide and rituximab but these are generally used in combination with an aggressive antithrombotic strategy.[19]

Recently, major advances in understanding the pathophysiology of this syndrome have been made. The achievements in insight of the disease have opened the

door to the possibility of new more targeted therapeutic options that might be safer and more efficacious than the standard treatment modalities.[20] In this context, potential targeted therapeutic approaches have been proposed with promising results, including for example, hydroxychloroquine, statins, inhibition of β(2) GPI and/or anti-β(2) GPI binding to target cells, complement inhibition, and B cell inhibition.[21]

In conclusion, the diagnosis and treatment of a recurrent thromboembolic event in a patient with APS, adequately anticoagulated may not be linear.

We believe that the scientific advances in understanding the mechanisms of antiphospholipid antibody-mediated thrombosis are driving us to a potentially new immunosuppressive combined approach. New therapeutic strategies have been proposed, showing that much more can be done in the near future.

Learning points

- The diagnosis and treatment of a recurrent thromboembolic event in a patient with APS, adequately anticoagulated may not be linear.
- The recurrence of thrombotic events affects only a minority of patients with APS, despite adequate anticoagulation.
- Additional thrombosis risk factors should be controlled and prevented in patients with APS.
- Especially in secondary APS cases, associated with another autoimmune disease, an immunomodulatory therapeutic strategy could be considered, beyond anticoagulation.

Competing interests None.

Patient consent Obtained.

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